Dynamic relations between longitudinal morphological, behavioral, and emotional indicators and cognitive impairment: evidence from the Chinese Longitudinal Healthy Longevity Survey

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Abstract

Background: We aimed to assess the effects of body mass index (BMI), activities of daily living (ADL), and emotional status (EMO) on cognitive impairment (CI) and propose dynamic risk prediction models for CI.

Methods: We leveraged the Chinese Longitudinal Healthy Longevity Survey from 1998 to 2018. Cognitive status was measured using the Chinese Mini-Mental State Examination. We employed repeated measures correlation to assess associations, linear mixed-effect models to characterize the longitudinal changes, and Cox proportional hazard regression to model survival time. Dynamic predictive models were established based on the Bayesian joint model and deep learning approach named dynamic-DeepHit. Marginal structural Cox models were adopted to control for time-varying confounding factors and assess effect sizes.

Results: ADL, EMO, and BMI showed protective effects on CI after controlling for observed confounding factors, with respective direct hazard ratios of 0.044 (0.036, 0.053), 0.034 (0.026, 0.045), and 0.899 (0.891, 0.908). Dynamic risk predictive models manifested high accuracy (best AUC=0.91). ADL was endowed with the best predictive capability, although the combination of BMI, ADL, and EMO showed the most remarkable performance.

Conclusions: BMI, ADL, and EMO are protective factors for CI. A dynamic prediction model using these indicators can efficiently identify vulnerable individuals with high accuracy.

Keywords: aging cognitive impairment; dynamic risk prediction; deep survival model; longitudinal causal inference; body mass index; activities of daily living; emotional status

1. Background

The rapid escalation of aging has become a crucial global concern, entailing daunting challenges that place a substantial burden, especially within the realm of public health (1). With the proportion of individuals aged 65 and above reaching 17.4% in 2020 (2), China has emerged as the nation with the largest and most rapidly expanding elderly population, signifying the significant growth of aging demographics.

Despite significant achievements, the increasingly aging society still causes great challenges, including labor shortages, expanding government spending, and inadequate and unevenly distributed health care systems (3). Compared to physical needs, the mental health of older adults has not received sufficient attention (4). Older adults are susceptible to a series of mental and psychological problems, and cognitive impairment (CI) is a common example. It is estimated that there are approximately 36 million people suffering from CI worldwide, and this number is expected to reach 115 million by 2050 (5). Half of patients with mild CI will develop severe impairment or even dementia within 5 years (6). A better understanding of risk factors is necessary to ameliorate this problem.

Several risk factors related to CI have been reported, including activities of daily living (ADL) (Gao et al., 2017) and emotional status (EMO) (Z. Ismail et al., 2017; Zahinoor Ismail, Malick, Smith, Schweizer, & Fischer, 2014). However, the effect sizes remain unclear due to the existence of potential coaction among these indicators and other potential confounding factors. In addition, the role of body mass index (BMI) is particularly confusing, since some reported that a decline in BMI is an alarm of cognitive disorders (2, 3, 7-12), while others suggested that lower BMI decreases the risk of CI (13, 14). Therefore, in this study, we aimed to comprehensively assess the effect of BMI, ADL, and EMO on CI and establish a dynamic predictive model for early screening.

The Cox proportional hazard model is commonly adopted for effect estimation and risk prediction in survival analysis, where the proportional odds of hazard functions are assumed to be constant over time. Nevertheless, the estimates may be biased (15) when tackling longitudinal covariates due to the existence of multiple time-fixed and time-varying confounding factors. As time-varying indicators participate in the cognition decline process during aging, it is inefficient to model the longitudinal and survival outcomes separately. Additionally, the Cox model solely relies on baseline covariates to predict hazard, disregarding valuable information contained within the longitudinal history. However, the dynamic changes observed between follow-up periods often serve as crucial indicators for disease onset.

In this study, to assess the effects of risk factors and use the identified factors to establish dynamic risk prediction models for CI, we leveraged evidence from the Chinese Longitudinal Healthy Longevity Survey (CLHLS) (16), a long-term, large-scale Chinese cohort study. We leveraged a linear mixed-effect model (LMM), repeated measures correlation (rmcorr), time-dependent Cox regression, and Bayesian joint model to examine the association of BMI, ADL, and emotion index (EMO) with CI. With data from the CLHLS, we employed a Bayesian joint model and deep learning-based longitudinal survival model to evaluate the predictive performance using the longitudinal history of these indicators. We finally evaluated hazard ratios (HRs) using a marginal structural Cox model (Cox-MSM) to control for observed time-varying confounding.

2. Methods

2.1 Study design and participants

The CLHLS was conducted with eight waves from 1998 to 2018 in 23 out of 31 provinces with approximately 130,000 recodes. This survey has the largest coverage, the longest tracking time, the most complete data, and the greatest social influence in the field of longevity health in China. Participants over 80 were recruited in the first two waves, and older adults over 65 were included from 2002. Details of the participants in each wave can be found in Supplementary Table S2. The questionnaire contained seven core parts: the participants' basic information; self-evaluation of their health, personality, and emotional characteristics; cognitive ability; lifestyle; ability to perform daily activities; personal background and family structure; and physical health (17). We deleted the records without cognitive information, and 40,087 samples with 83,994 records were included in this study.

2.2 Measures

BMI, defined as weight (in kilograms) divided by the square of height (in meters), is a commonly used morphological indicator (18). For the first four waves, height was converted from knee height (height = 0.6778 + 2.01 × knee height for men~~,~~ and height = 0.7408 + 1.81 × knee height for women) or interpolated from the average of the two most recent height measurements.

ADL is a self-reported indicator, where each respondent was asked about their ability to perform the daily activities of bathing, dressing, toileting, indoor mobility, bowel control, and eating. Scores were assigned based on their reported completion of these activities (independent-2; required assistance from 1 person-1; required assistance from 2 or more people-0), and ADL is the sum of each item.

EMO was measured using the Centre for Epidemiological Survey Depression Scale (CES-D scale) in the CLHLS questionnaire, representing the respondent's mood condition (19). We simply assign +1 for positive questions and -1 for negative questions. For convenience, we scaled both ADL and EMO to a score ranging from 0 to 1.

Cognitive status was measured using the Chinese Mini-Mental State Examination (CMMSE) (20), revised from the commonly used Mini-Mental State Examination (MMSE) (21) to adapt to the Chinese population (Supplementary Table

S1). The final score varied from 0 to 30, with a lower score representing worse cognitive ability. Since most of the participants had received little or no education, individuals with scores lower than 18 were identified as CI patients (22).

2.3 Association Analysis

We utilized LMM to describe overall trends in longitudinal covariates. In addition to the conventionally used Pearson and Spearman correlations, we used rmcorr (23), a longitudinal correlation coefficient based on analysis of covariance (ANCOVA), to determine the relationships between CMMSE scores and longitudinal indicators. Both time-invariant (using baseline information only) and time-dependent Cox proportional hazard regressions were used to assess the effects of covariates on CI risk, where the latter is assumed the covariate's effect on the outcome is constant over the follow-up time to meet the requirement of proportional hazards assumption (24).

The joint model is a statistical framework integrating both longitudinal and survival submodels by imposing an association function $\omega(\cdot)$ to link the longitudinal responses in the LMM as explanatory covariates in survival analysis (25). To simplify the model, we assumed that the hazard function at each time related to the current value of longitudinal variables and HR remained the same for each time point. Therefore, we adopt the following model:

$$y_i(t) = m_i(t) + \varepsilon_i(t) = (\beta_0 + b_{i0}) + (\beta_1 + b_{i1})t_i + \varepsilon_i(t),$$

$$h(t|\omega_i, M_i(t)) = h_0(t)\mathrm{e}^{\gamma^T\omega_i + \alpha\omega[m_i(t)]} = h_0(t)\mathrm{e}^{\gamma^T\omega_i + \alpha m_i(t)},$$

where $y_i(t)$ represents the observed longitudinal outcome at time t for individual i, $m_i(t)$ is the part that can be explained by the LMM, ω_i stands for the baseline time-independent covariates of individual i, and $h(t)$ represents the hazard function.

We conducted 10-fold cross-validation to evaluate the prediction performance of the baseline Cox model and Bayesian joint models. Time-dependent areas under the receiver operating characteristic curves (AUCs) for baseline Cox models were examined using both incident sensitivity and cumulative sensitivity (26). The AUCs of joint models are predicted in time window $(t,\ t + \Delta t)$ using longitudinal history from inclusion until time t for those who survive at time t.

Cox regression, LMM, and rmcorr were conducted using the R packages survival, nlme, and rmcorr. The Bayesian joint model was established using the R package JMbayes, which uses Markov chain Monte Carlo (MCMC) algorithms to attain the posterior estimation of the joint model. All of the reported probabilities are two-sided.

2.4 Deep Learning-Based Dynamic Predictive Model

The Bayesian joint model confronted tricky problems in computation when coping with a large sample size and multivariate longitudinal outcomes. Therefore, we introduce dynamic-DeepHit, a deep learning-based approach to predict the cumulative incidence function (CIF) according to the longitudinal history (27). It utilizes a recurrent neural network (RNN) module, a gated recurrent unit (GRU), and a temporal attention mechanism to extract the longitudinal features and assign weights to different measurements. The extracted features are then imported to train a feed-forward network by minimizing the total loss function, which is defined as a combination of a log-likelihood loss to capture the first hitting time, a ranking loss to adapt the requirement of concordance, and an RNN prediction loss to enhance the ability of longitudinal feature extraction. The time-dependent concordance index (C-index) $C(t, \Delta t)$ (27) was used to examine the discrimination performance of dynamic-DeepHit, defined by comparing two participants' estimated CIFs at time $t + \Delta t$ based on the longitudinal history from baseline to time t. We implemented the deep learning-based analysis with TensorFlow, and details can be found in the methodology Appendix.

2.5 Longitudinal Causal Inference with the Marginal Structure Cox Model

We resorted to the marginal structure model (MSM) (28, 29) to inspect whether the correlation between these indicators and cognitive ability could be attributed to causality. When evaluating a longitudinal indicator's (e.g., ADL) direct effect on CI, we controlled both baseline demographic characteristics (as time-fixed covariates V_i) and two other indicators (as time-varying confounding L_{ij}, e.g., EMO and BMI) by imposing stabilized inverse-probability weights (IPWs) on each sample. The weights were estimated via generalized estimating equation (GEE) models, and the weighted "pseudopopulation" was then fitted into Cox-MSMs (30) so that the average causal HR could be estimated. The causal analysis was implemented with the R package IPW (31, 32).

3. Results

3.1 Descriptive analysis

A total of 40,087 samples were included in the analysis. As shown in Table 1, in the CI group, the proportions of women, people living in rural areas, people with manual labor occupations, and people who were single were all higher than those in the control group. The participants ending up with CI also had a higher average age and lower average number of years of education. Compared to the CI group, participants in the non-CI group had a higher BMI, ADL, and EMO as well.

We first used the baseline data to conduct a time-invariant correlation analysis. Various factors were revealed to be related to CI (Supplementary Table S3, Supplementary Figure S2), and these factors were also interrelated (Supplementary Figure S1). Generally, single people with older age, shorter education periods, lower BMI, living in rural areas and less engaged in mental labor were more likely to suffer from CI. Insufficient ability to perform daily activities and depressed mood were also related to an increased risk of CI.

Figure 1 shows the changes in BMI, ADL, and emotional condition for participants with at least 3 follow-ups, as well as the rmcorr plots between the three indicators and CMMSE score. It is obvious that a decreasing trend of ADL can be found in both groups, while ADL dipped far dramatically in the CI group, and the average ADL in the non-CI group was higher than that of the CI group. Correlation analysis further supported the positive association between ADL and cognitive status [rmcorr r = 0.37 (0.35, 0.38), P < 1e-16]. A positive correlation also existed between emotional and cognitive status [rmcorr r = 0.13 (0.10, 0.16), P < 1e-16]. A remarkable rise in EMO can be observed in the non-CI group, which may be related to the development of China's economy and the improvement of living standards during the follow-up period, while the overall trend in the CI group remained almost constant. Although an increase in BMI was noted for both groups, the average BMI in the non-CI group remained higher than that in the CI group, with a slight correlation reported between BMI and CMMSE score [rmcorr r = 0.02 (0.002, 0.04), P = 0.026].

3.2 Bayesian joint models show remarkable discriminant performance

BMI, ADL, and EMO were used as single longitudinal response variables in three joint models. Samples without records of the corresponding longitudinal variables were removed. As shown in Table 2, ADL and EMO both showed negative HRs for CI. Older adults with a weaker ability to perform daily activities and more depressed mood were more likely to develop CI. Additionally, the results suggested that lower BMI increased the risk of CI as well, although with a slightly lower size [β = −0.1070 (−0.1405, −0.0740), $P < 0.01$]. Subgroup analyses indicate that the three longitudinal indicators have more dominant effects on the CI risk of females than males (Supplementary Tables S5-S7), and older adults of advanced age (baseline age ≥ 80) are more sensitive to ADL and EMO than those younger (Supplementary Tables S8-S10).

We used 10-fold cross validation to evaluate the dynamic AUCs of the baseline Cox model in terms of both incident and cumulative sensitivities (26) (Figure 2a). Then, 10-fold cross-validation was used to examine the dynamic prediction performance of joint models including subjects with at least two follow-up records (Figure 2b). All three indicators show remarkable discriminant abilities in the joint models, especially when longitudinal records of the past 10 years were used to predict the status in the next 2 years, and the AUC reached 0.91. To our surprise, using fewer historical records or predicting in a longer time window will not reduce the accuracy monotonically. This is likely to be attributed to a decrease in sample size when modeling and evaluating over a longer time period. Overall, the morphological, behavioral, and emotional indicators exhibit a substantial and enduring ability to discriminate CI, with ADL emerging as the most informative predictor.

3.3 Deep survival models suggest indicator interaction

Despite the theoretical feasibility, the Bayesian joint models failed to model the three longitudinal indicators simultaneously due to computational burdens. As a complement, dynamic-DeepHit, involving baseline demographic characteristics and the combinations of three longitudinal indicators as predictors, was introduced to further examine how the longitudinal indicators incorporate each other. Participants with over two records on ADL, BMI, and EMO were filtered into the model. As shown in Figure 2c, the collaboration of all three indicators manifested a considerable prediction accuracy (with a C-index over 0.8). Compared to the benchmark, ADL, BMI, and EMO all boosted the model's discriminant ability, while ADL made the most remarkable contribution, similar to the findings in the joint model. While mood status alone demonstrated relatively weak predictive power for cognitive decline, the addition of EMO yielded greater improvement in prediction performance compared to the inclusion of BMI when ADL was already present in the model. This finding suggested potential interactions among mood, motor ability, and cognition.

3.4 Marginal structure Cox models estimate effect sizes by controlling observed confounding

Both baseline (Figure 3a) and time-dependent Cox models (Figure 3b) manifested the protective effects of ADL, EMO, and BMI, although with a smaller effect. However, the existence of coactions among these factors, as indicated by the dynamic DeepHit models above, might damage the effect estimation.

As a consequence, we then explored the direct effect of each longitudinal indicator by adopting Cox-MSMs to control both static and time-varying confounding. When evaluating a particular indicator's effect, we regarded other covariates and indicators as confounding to calculate the stabilized IPW. All three indicators suggested significant direct effects (Figure 3c). ADL and EMO showed strong protective effects, but the effect of BMI was weaker. We conducted subset analysis according to sex and baseline age to explore population heterogeneity. ADL and EMO show more remarkable protective effects on cognition in males and younger aging populations (age<80), while BMI's effect is slightly larger in females and younger aging populations.

The results provided evidence of causality under the assumption of no unobserved confounding, which indicated that longitudinal morphological, behavioral, and emotional indicators could be regarded not only as predictors but also as potential treatment targets, discussed thoroughly in the discussion section.

4. Discussion

It is widely acknowledged that physical, behavioral, emotional, and cognitive status link each other tightly during the aging process. Our work supported the idea that older adults with weak ADL ability and depressed mood are at a higher risk of CI and identified higher BMI as a protective factor for cognitive ability. The cross-validation results of the Bayesian joint models and dynamic-DeepHit show that the three indicators, ADL in particular, are easily assessed and well-informed predictors of cognitive decline. The decrease in BMI, ADL, and EMO is a sign of cognitive decline for aging people, making it possible to identify vulnerable populations and take measures to prevent deterioration in time.

The correlations between predictors may bias the inference and cause misleading explanations. For example, women seem to be at a higher risk of CI than men, yet the higher rate of CI in women may actually result from their higher life expectancy or relatively fewer educational opportunities instead of mere sex differences. We resorted MSMs to control measured confounding factors and identify each indicator's direct effect magnitudes.

The results of the marginal structural Cox model also provided clues for the existence of causality under the assumption of no unobserved confounding. Although the conclusion of causality from observational studies should be regarded with caution and needs more evidence from triangulation (33), the protective effects of BMI, ADL, and EMO on CI revealed by this study supported the idea of preventing cognitive decline via nonpharmacological interventions, such as emotion therapy or morphological management. Some particular negative emotions, such as loneliness and depression, were reported to be linked to cognitive decline in older adults (34-36). Recent studies revealed that positive beliefs promoted patients to recover from mild

CI (37), and aging brains showed more remarkable emotional carryover effects (emotional inertia) after exposure to negative socioemotional events, which affected activity patterns in regions such as the posterior cingulate cortex (PCC), resulting in an increased risk of neurodegenerative diseases (38).

The strengths of this research are obvious. The CLHLS is so far the largest study with the longest follow-up on the health of older adults in China, geographically widespread and fully representative of the Chinese population. Furthermore, in addition to the baseline information, time-varying data during the follow-ups were fully exploited. We examined the longitudinal morphological, behavioral, and emotional indicators' effects on cognitive decline via several different approaches, including MSMs controlling measurable confounding, following the idea of triangulation (39). Dynamic risk prediction models, implemented with Bayesian joint models and deep neural networks, integrated time-varying information efficiently and achieved remarkable accuracy.

However, the analysis still has some drawbacks. The use of the longitudinal model brings computational burdens, especially for large sample sizes and limited follow-up times. Issues such as participants' death, failure in follow-up, and measurement errors reduce the number of longitudinal records. Due to the presence of unobserved confounding, identifying the causal effects in a time-varying process is still tricky. Incorporating additional information, such as genetic anchors, and approaches such as time-varying Mendelian randomization (40) can avoid the interference of unmeasured confounding and strengthen causal inference.

5. Conclusion

In conclusion, evidence from a large-scale, long-term cohort study supports that changes in ADL, EMO, and BMI are closely associated with cognitive decline in older Chinese adults, especially in male and younger aging populations. By controlling for time-fixed and time-varying confounding factors, ADL, EMO, and BMI all showed significant protective effects on cognitive decline. Using longitudinal history, Bayesian joint models and deep survival models manifest a remarkable predictive performance on CI. The integration of three indicators boosts the performance, and ADL is the most informative predictor.

List of abbreviations

CI: cognitive decline

BMI: body mass index

ADL: activities of daily life

EMO: emotion index

CLHLS: Chinese Longitudinal Healthy Longevity Survey

MSM: marginal structure model

LMM: linear mixed-effect model

AUC: area under the receiver operating characteristic curve

IPW: inverse-probability weights

GEE: generalized estimating equation

RNN: recurrent neural network

GRU: gated recurrent unit

CIF: cumulative incidence function

rmcorr: repeated measure correlation coefficient

Declarations

Ethics approval and consent to participate: The CLHLS study was approved by the Research Ethics Committee of Peking University (IRB00001052–13074), and all participants or their proxy respondents provided written informed consent.

Consent for publication: Not applicable.

Availability of data and materials: The dataset supporting the conclusions of this article is available at https://opendata.pku.edu.cn/dataverse/CHADS.

Supplementary data: Supplementary data are available online.

Author contributions: JS and YZ designed the study. YZ supervised and sponsored the study. JS conducted the analysis and wrote the manuscript. LD helped manage the data. JS, LD, QL, JZ, and YZ discussed and revised the manuscript.

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Reference

1. Ogura S, Jakovljevic MM. Global population aging-health care, social and economic consequences. Frontiers in public health. 2018;6:335.
2. Hou Q, Guan Y, Yu W, Liu X, Wu L, Xiao M, et al. Associations between obesity and cognitive impairment in the Chinese elderly: an observational study. Clin Interv Aging. 2019;14:367-73.
3. Cao Z, Xu C, Yang H, Li S, Xu F, Zhang Y, et al. Associations of BMI and Serum Urate with Developing Dementia: A Prospective Cohort Study. The Journal of Clinical Endocrinology & Metabolism. 2020;105(12):e4688-e98.
4. Zhang Q-E, Ng C, Ungvari G, Van I, Wang G, Xiang Y. Mental Health-Care Delivery for Older People in China: An Update of Challenges and Recent Clinical Research. Journal of Geriatric Psychiatry and Neurology. 2019;32:287 - 90.
5. Wortmann M. Dementia: a global health priority - highlights from an ADI and World Health Organization report. Alzheimer's Research & Therapy. 2012;4:40 -
6. Ng T, Feng L, Nyunt M, Feng L, Gao Q, Lim M, et al. Metabolic Syndrome and the Risk of Mild Cognitive Impairment and Progression to Dementia: Follow-up of the Singapore Longitudinal Ageing Study Cohort. JAMA neurology. 2016;73 4:456-63.
7. Alhurani RE, Vassilaki M, Aakre JA, Mielke MM, Kremers WK, Machulda MM, et al. Decline in Weight and Incident Mild Cognitive Impairment: Mayo Clinic Study of Aging. JAMA Neurol. 2016;73(4):439-46.
8. Coin A, Veronese N, De Rui M, Mosele M, Bolzetta F, Girardi A, et al. Nutritional predictors of cognitive impairment severity in demented elderly patients: The key role of BMI. The journal of nutrition, health & aging. 2012;16(6):553-6.
9. Pedditizi E, Peters R, Beckett N. The risk of overweight/obesity in mid-life and late life for the development of dementia: a systematic review and meta-analysis of longitudinal studies. Age and Ageing. 2016;45(1):14-21.
10. Buchman AS, Wilson RS, Bienias JL, Shah RC, Evans DA, Bennett DA. Change in body mass index and risk of incident Alzheimer disease. Neurology. 2005;65(6):892.

11. Atti AR, Palmer K, Volpato S, Winblad B, De Ronchi D, Fratiglioni L. Late-Life Body Mass Index and Dementia Incidence: Nine-Year Follow-Up Data from the Kungsholmen Project. Journal of the American Geriatrics Society. 2008;56(1):111-6.
12. Qizilbash N, Gregson J, Johnson ME, Pearce N, Douglas I, Wing K, et al. BMI and risk of dementia in two million people over two decades: a retrospective cohort study. Lancet Diabetes Endocrinol. 2015;3(6):431-6.
13. Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kåreholt I, Winblad B, et al. Obesity and Vascular Risk Factors at Midlife and the Risk of Dementia and Alzheimer Disease. Archives of Neurology. 2005;62(10):1556-60.
14. Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth WT, Jr., et al. Midlife and Late-Life Obesity and the Risk of Dementia: Cardiovascular Health Study. Archives of Neurology. 2009;66(3):336-42.
15. Ibrahim JG, Chu H, Chen LM. Basic concepts and methods for joint models of longitudinal and survival data. Journal of Clinical Oncology. 2010;28(16):2796-801.
16. Zeng Y, Feng Q, Hesketh T, Christensen K, Vaupel JW. Survival, disabilities in activities of daily living, and physical and cognitive functioning among the oldest-old in China: a cohort study. Lancet. 2017;389(10079):1619-29.
17. Zheng Z. Twenty years' follow-up on elder people's health and quality of life. China Population and Development Studies. 2020;3(4):297-309.
18. Flegal KM, Williamson DF, Pamuk ER, Rosenberg HM. Estimating Deaths Attributable to Obesity in the United States. American Journal of Public Health. 2004;94(9):1486-9.
19. Lei X, Bai C. Cognitive function and mental health of elderly people in China: findings from 2018 CLHLS survey. China Population and Development Studies. 2020;3(4):343-51.
20. Chiu H, Lee H-cB, Chung WS, Kwong PK. Reliability and Validity of the Cantonese Version of Mini-Mental State Examination-A Preliminary Study. Hong Kong Journal of Psychiatry. 1994;4:25.
21. Creavin S, Wisniewski S, Noel-Storr A, Trevelyan CM, Hampton T, Rayment D, et al. Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. The Cochrane database of systematic reviews. 2016;1:CD011145.
22. Yu R, Morley JE, Kwok T, Leung J, Cheung O, Woo J. The Effects of Combinations of Cognitive Impairment and Pre-frailty on Adverse Outcomes from a Prospective Community-Based Cohort Study of Older Chinese People. Front Med (Lausanne). 2018;5:50.
23. Bakdash JZ, Marusich LR. Repeated measures correlation. Frontiers in psychology. 2017;8:456.
24. Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models. Annals of Translational Medicine. 2018;6(7):121.
25. Baghfalaki T, Ganjali M, Berridge D. Joint modeling of multivariate longitudinal mixed measurements and time to event data using a Bayesian approach. Journal of Applied Statistics. 2014;41:1934 - 55.
26. Kamarudin AN, Cox T, Kolamunnage-Dona R. Time-dependent ROC curve analysis in medical research: current methods and applications. BMC Medical Research Methodology. 2017;17(1):53.

27. Lee C, Yoon J, Van Der Schaar M. Dynamic-deephit: A deep learning approach for dynamic survival analysis with competing risks based on longitudinal data. IEEE Transactions on Biomedical Engineering. 2019;67(1):122-33.
28. Hernán MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology. 2000;11(5):561-70.
29. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology. 2000;11(5):550-60.
30. Karim ME, Gustafson P, Petkau J, Zhao Y, Shirani A, Kingwell E, et al. Marginal structural Cox models for estimating the association between β-interferon exposure and disease progression in a multiple sclerosis cohort. American Journal of Epidemiology. 2014;180(2):160-71.
31. van der Wal WM, Geskus RB. ipw: An R Package for Inverse Probability Weighting. Journal of Statistical Software. 2011;43(13):1 - 23.
32. Zhang Z, Jin P, Feng M, Yang J, Huang J, Chen L, et al. Causal inference with marginal structural modeling for longitudinal data in laparoscopic surgery: A technical note. Laparoscopic, Endoscopic and Robotic Surgery. 2022;5(4):146-52.
33. Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. Int J Epidemiol. 2016;45(6):1866-86.
34. Zhong BL, Chen SL, Conwell Y. Effects of Transient Versus Chronic Loneliness on Cognitive Function in Older Adults: Findings From the Chinese Longitudinal Healthy Longevity Survey. The American Journal of Geriatric Psychiatry. 2016;24(5):389-98.
35. Gordilho de Souza J, Souza Farias-Itao D, Aliberti MJR, Bertola L, Bof de Andrade F, Fernanda Lima-Costa M, et al. Social isolation, loneliness, and cognitive performance in older adults: Evidence from the ELSI-Brazil study. The American Journal of Geriatric Psychiatry. 2023.
36. Monin JK, McAvay G, Newkirk K, Samper-Ternent R. Longitudinal associations between cognitive functioning and depressive symptoms among couples in the Mexican Health and Aging Study. International Psychogeriatrics. 2023:1-11.
37. Levy BR, Slade MD. Role of Positive Age Beliefs in Recovery From Mild Cognitive Impairment Among Older Persons. JAMA Network Open. 2023;6(4):e237707-e.
38. Baez-Lugo S, Deza-Araujo YI, Maradan C, Collette F, Lutz A, Marchant NL, et al. Exposure to negative socio-emotional events induces sustained alteration of resting-state brain networks in older adults. Nature Aging. 2023;3(1):105-20.
39. Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. International Journal of Epidemiology. 2017;45(6):1866-86.
40. Shi J, Swanson SA, Kraft P, Rosner B, De Vivo I, Hernán MA. Mendelian Randomization With Repeated Measures of a Time-varying Exposure: An Application of Structural Mean Models. Epidemiology. 2022;33(1):84-94.

Table 1 Descriptive statistics of baseline demographic characteristics and indicator values

	CI (outcome = 1)	Non-CI (outcome = 0)	All
Sex			
Female (0)	73.67%	50.50%	57.13%
Male (1)	26.33%	49.50%	42.87%
Age			
Mean	93.62	84.48	87.09
Resident			
Rural (0)	64.27%	56.35%	58.33%
Urban (1)	35.73%	44.05%	41.67%
Years of education			
Mean	0.7602	2.490	1.997
Occupation			
Physical (0)	97.63%	90.50%	92.54%
Mental (1)	2.37%	9.50%	7.46%
Marital status			
Never married (0)	0.96%	1.24%	1.16%
Married but currently single (1)	86.54%	63.70%	70.23%
Currently married (2)	12.50%	35.06%	28.61%
ADL			
Mean	0.8430	0.9560	0.9250
EMO			
Mean	0.6320	0.6880	0.6750
BMI			
Mean	18.99	20.37	19.97
Total number	11,464 (28.60%)	28,623 (71.40%)	40,087

Table 2 Dynamic associations measured by the Bayesian joint model[a]

	BMI coefficient	P value[b]	ADL coefficient	P value	EMO coefficient	P value
Sex	−0.2233 (−0.2940, −0.1667)	< 0.001	−0.0752 (−0.1306, −0.0142)	0.011	−0.2703 (−0.3151, −0.2168)	< 0.001
Age	0.0692 (0.0603, 0.0732)	< 0.001	0.0889 (0.0854, 0.0943)	< 0.001	0.1143 (0.1109, 0.1184)	< 0.001
Residence	−0.1596 (−0.2263, −0.1027)	< 0.001	−0.1695 (−0.2172, −0.1199)	< 0.001	−0.0063 (−0.0564, 0.0405)	0.868
Education	−0.0918 (−0.1064, −0.0794)	< 0.001	−0.1017 (−0.1126, −0.0899)	< 0.001	−0.0911 (−0.1007, −0.0793)	< 0.001
Occupation	−0.1556 (−0.3228, 0.0064)	0.060	−0.2024 (−0.3555, −0.0487)	0.012	−0.1682 (−0.2974, 0.0302)	0.107
Marital status	−0.4223 (−0.6190, −0.3085)	< 0.001	−0.3538 (−0.4200, −0.2932)	< 0.001	−0.3315 (−0.3895, −0.2793)	< 0.001
Dynamic association	−0.1070 (−0.1405, −0.0740)	< 0.001	−4.3604 (−4.6484, −4.0931)	< 0.001	−0.2497 (−0.3860, −0.1834)	< 0.001
Sample size	32,583		33,763		30,322	

[a] There are 20,000 iterations in each joint model. The dynamic association in the table corresponds to the coefficients of BMI, ADL, and EMO. BMI is normalized in the model. The values in parentheses correspond to 95% confidence intervals.

[b] P values are calculated as $2 \times \min\{P(\theta > 0), P(\theta < 0)\}$, where θ represents the corresponding regression coefficient in the joint model.

Figure legends

Figure 1 Changes and correlations of longitudinal covariates over years. Changes in ADL (a), EMO (c), and BMI (e) after baseline. The gray lines represent the trajectories of each individual, the blue line represents the average trend estimated through the linear mixed-effect model, and the cyan shading represents the confidence interval of the average trend. Repeat measures correlation plot between CMMSE scores and ADL (b), EMO (d), and BMI (f).

Figure 2 Prediction performance of baseline Cox models (a), Bayesian joint models (b), and dynamic-DeepHit (c). a. The prediction AUCs of the baseline Cox model in 10-fold cross-validation. Time-dependent AUCs for both incident sensitivity (solid) and cumulative sensitivity (dashed) are shown. b. The prediction AUCs of the joint model. The AUCs are predicted at time $t + \Delta t$ using measurements until time t for those who survive at time t after inclusion. The horizontal axis is the evaluated time interval Δt, and the vertical axis is the mean AUC of the 10-fold cross-validation. c. The dynamic C-index of dynamic-DeepHit, estimated at time $t + \Delta t$ based on the longitudinal history from baseline to time t. ADL: ability of daily living; BMI: body mass index; EMO: emotion index. Benchmark: dynamic-DeepHit with baseline demographic characteristics only.

Figure 3 Results of the time-invariant Cox model for baseline data (a), time-dependent Cox model using longitudinal covariates (b), and Cox-MSMs (c). The scale represents the HRs and corresponding 95% confidence intervals. Figure 3c illustrates the direct effect of each longitudinal indicator by controlling baseline demographic characteristics and the other two indicators, estimated through MSMs. res: residence, edu: years of education years, occ: occupation, mar: marital status, ADL: ability of daily living; BMI: body mass index; EMO: emotion index.